



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0842]

Gluten in Drug Products; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for information and comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing the establishment of a docket to obtain information and comments that will assist the Agency in its deliberations about ways to help individuals with celiac disease avoid the presence of gluten in drug products. In particular, FDA is interested in information on ingredients present in human drug products marketed in the United States that are currently derived from wheat, barley, or rye.

DATES: Submit either electronic or written information and comments by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit electronic information and comments to <http://www.regulations.gov>. Submit written information and comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify both electronic and written comments and any supporting documents with the docket number in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

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#### SUPPLEMENTARY INFORMATION:

##### I. Background

##### A. Celiac Disease

Celiac disease (also known as celiac sprue and gluten-sensitive enteropathy) is an immune-mediated chronic inflammatory disorder affecting primarily the small intestine in genetically susceptible individuals (Refs. 1 and 2). In these individuals, the symptoms of celiac disease are triggered by the ingestion of wheat grain proteins collectively known as gluten (Ref. 3). The consumption of wheat gluten and similar proteins in barley and rye stimulates the production of antibodies and inflammatory cells, resulting in an abnormal immune response. The resultant immediate inflammatory reaction damages the tiny, fingerlike protrusions called "villi" that line the small intestine and absorb nutrients from food (Refs. 4 and 5). In addition, over time, continued dietary exposure to gluten from wheat, barley, or rye can lead to impaired absorption of nutrients and a variety of other serious health problems (Ref. 4). For the purposes of this notice, the phrase "wheat, barley, or rye" includes wheat, barley, and rye, as well as the crossbred hybrids of these grains.

The prevalence of celiac disease in the United States is estimated to range from about 0.4 percent to about 1 percent of the population (Refs. 1 and 6). Celiac disease may go undetected in some individuals for years before they develop symptoms that cause them to seek medical attention (Refs. 7 and 8).

The standard treatment of celiac disease is the elimination of gluten-containing products from the diet (Ref. 1). Over time, strict avoidance of gluten from wheat, barley, or rye sources can resolve the symptoms, mitigate and possibly reverse intestinal damage, and reduce the health risks associated with celiac disease (Ref. 4). For some individuals with celiac disease, over time, failure to avoid consumption of gluten from wheat, barley, and rye can lead to severe and sometimes life-threatening complications (Refs. 9 to 11).

#### B. Gluten and Grains of Concern for Individuals With Celiac Disease

Technically, "gluten" is the storage protein of wheat that is composed of alcohol-soluble gliadins and insoluble glutenins (Ref. 2). Gliadins have been most closely studied and have been found to be the main antigen in celiac disease; however, glutenins also have been implicated in the disease (Refs. 12 and 13). The storage proteins of rye (secalins) and barley (hordeins) are similar in amino acid sequence to wheat gluten proteins and may trigger the same inflammatory response. For these reasons, the term "gluten" has been adopted to mean any proteins implicated in celiac disease (Ref. 2). In this notice, the term "gluten" is used to refer to the antigenic proteins of wheat, barley, and rye implicated in celiac disease.

The grains that contain gluten that can cause harm to individuals who have celiac disease are as follows: Wheat (including durum wheat, spelt wheat, and kamut), barley, rye, and crossbred hybrids of these grains (e.g., triticale, which is a cross between wheat and rye) (Refs. 14 and 15). While there is no general agreement among experts about the extent to which oats may present a hazard for individuals who have celiac disease (Refs. 16 to 18), it is generally believed that moderate amounts of oats can be ingested safely by the majority of individuals with celiac disease (Ref. 4).

### C. Determination of Tolerable Daily Intake

The extent of risk posed to celiac patients by ingestion of trace amounts of gluten is uncertain. The majority of current data is from retrospective studies or nonrandomized, prospective, nonblinded studies without a placebo challenge group, limiting the conclusive evidence on safe thresholds for gluten intake. In the context of an ongoing rulemaking to define criteria for voluntary "gluten-free" claims on food, FDA's Office of Food Safety in the Center for Food Safety and Applied Nutrition undertook a health hazard assessment for gluten exposure in individuals with celiac disease.

The assessment, which is available for public review (Ref. 19), included a description and characterization of available prospective dose-effect data, as well as a safety assessment derived from prospective gluten challenge data from individuals with celiac disease. The assessment specifically examined morphological and clinical adverse effects that are reflective of celiac disease. These reactions were subsequently placed into subgroups identifying whether they occurred after acute, subchronic, or chronic exposures. The no observable adverse effect level and lowest observable adverse effect level were determined for each study considered. Uncertainty factors were applied to account for limitations in data, variability in response between patients, and other potential gaps, and from this information tolerable daily intake levels of exposure were derived. Based on this health hazard assessment, a conservative tolerable daily intake level for gluten in individuals with celiac disease is 0.4 milligrams (mg) gluten per day for adverse morphological effects and 0.015 mg gluten per day for adverse clinical effects.

### D. Ingredients at Issue

The Agency believes that wheat is not used to a significant extent in the production of drug ingredients and that barley and rye are used either rarely or not at all. FDA is aware,

however, that certain ingredients in drug products may be derived from wheat. For the purposes of this notice, the phrase "drug products" refers to all FDA-regulated human drug products marketed in the United States. These include prescription, nonprescription, biologic, and homeopathic drug products. The National Formulary includes a monograph for wheat starch. Some monographs in the National Formulary and the U.S. Pharmacopeia include statements that wheat or wheat starch may be used as source materials. Other monographs include statements that starch may be used as a source material without specifying the plant source of the starch.

This request for information and comment includes information on all drug ingredients that may be derived from wheat, barley, or rye--whether or not they are the subject of a compendial monograph. Examples of such ingredients that FDA is aware of include: Wheat starch, modified starch, pregelatinized starch, pregelatinized modified starch, sodium starch glycolate, dextrans, dextrin, caramel, dextrimaltose, malt, maltodextrin, gamma cyclodextrin, and wheat bran. Certain flavor ingredients also may be derived from wheat, barley, or rye.

This notice does not request information relating to the possible presence of gluten from wheat, barley, or rye in drug products at trace levels that may result from accidental contamination.

## II. Discussion and Approaches

### A. Discussion

FDA is considering ways to help individuals with celiac disease avoid the presence of gluten in drug products. In 2008, the Agency received a citizen petition from an individual asking that the Agency prohibit the addition of wheat gluten to drug products (Ref. 20). FDA has heard from other individuals and organizations in recent years asking that the Agency do

more to provide assurance to individuals who have celiac disease that drug products will not harm them.

Currently, the possible presence of gluten in drug products presents a difficult challenge for individuals who have celiac disease. Ingredient information provided on drug labels and information available to pharmacists and physicians may not indicate whether certain drug products contain gluten. Faced with uncertainty, some patients may forego important treatment.

The possible presence of gluten in drug products presents a challenge to individuals who have celiac disease that is different from the challenges associated with dietary gluten. For example, medication is sometimes needed on an urgent basis, not leaving time for an investigation into the drug's gluten content. In some cases, a patient with celiac disease may be unable to confirm the gluten-free status of a drug product and may have difficulty obtaining a product known to be manufactured without gluten.

#### B. Approaches

The Agency is evaluating various approaches for helping patients with celiac disease avoid the presence of gluten in drug products. While the Food Allergen Labeling and Consumer Protection Act of 2004 (Public Law 108-282, Title II) specifies the creation of a standard for voluntary "gluten free" labeling for foods (see 72 FR 2795, January 23, 2007; 76 FR 46671, August 3, 2011), other options may be preferable for drugs, given the distinct considerations they present. FDA is particularly interested in understanding what impact would result if the use of drug ingredients derived from wheat, barley, or rye were completely discontinued in human drugs. If interested stakeholders do not identify reasons why certain ingredients must be derived from wheat, barley, or rye--or why the flexibility to use these grains as ingredient sources is

important--discontinuing use of such ingredients may be attractive for its simplicity and effectiveness in addressing the issue.

### III. Requested Information and Comments Regarding FDA-Regulated Human Drug Products Marketed in the United States

Interested persons are invited to provide detailed comment on all aspects of this issue with respect to prescription, nonprescription, biologic, and homeopathic drug products. FDA is particularly interested in responses to the following questions.

#### A. Current Practice

1. What inactive ingredients used in drug products marketed in the United States today are derived from wheat, barley, or rye? Please identify specific ingredients derived from any of these sources.

2. Please provide any available information on the number of drug products that contain inactive ingredients derived from wheat, barley, or rye. What is the general prevalence of such inactive ingredients in the human drug supply?

3. To what extent are active ingredients derived from wheat, barley, or rye used in drug products?

4. Are certain ingredients derived from wheat, barley, or rye processed in a way that removes gluten? Please provide information concerning the certainty with which processing methods may remove or destroy gluten and identify any test methods used to confirm the absence of gluten. The Agency's interest extends to ingredients that may be derived from a variety of starch sources if they are sometimes derived from wheat. Sugar alcohols such as sorbitol, xylitol, maltitol, and mannitol may fall into this category.

5. Do manufacturers routinely test ingredients or drug products to determine whether gluten is present? If so, what test methods are used and what is their sensitivity?

#### B. Flexibility and Consequences

6. What negative consequences, if any, would arise from discontinuing the use of ingredients derived from wheat, barley, or rye in drug products? Are there certain applications for which an ingredient (inactive or active) must be derived from one of these grains for reasons related to physical properties, performance characteristics, safety, efficacy, availability, or reformulation burden, as well as other reasons?

#### C. Exposure Estimate

7. Is it possible to determine, with a high level of assurance, that certain drug ingredients derived from wheat, barley, or rye are free of gluten or would contribute only very dilute, insignificant, and nonharmful quantities of gluten to a drug product? If so, what scientific evidence supports such a determination?

#### D. Routes of Administration

8. FDA believes that the use of ingredients derived from wheat, barley, or rye in drugs administered orally presents a particular risk to individuals who have celiac disease, as compared to use of these ingredients in drugs dispensed in dosage forms intended for other routes of administration. FDA welcomes comments in this area. Are ingredients derived from wheat, barley, or rye presently used in drugs that are intended for nonoral routes of administration, such as topical, injectable, or ano-rectally administered drugs? Please submit any data or information on risks to celiac patients associated with nonoral exposure to ingredients derived from wheat, barley, or rye.



#### E. Incidental Addition of Gluten

9. FDA is primarily interested in ingredients derived from wheat, barley, or rye that are intentionally added to and intended to remain in the drug product. However, the Agency welcomes responses to the following question: Are processing aids or production aids (e.g., filtration media or fermentation media) derived from wheat, barley, or rye used today that could introduce gluten into a drug product at nontrivial levels?

#### IV. Submission of Information and Comments

Interested persons may submit information and comments responsive to this request to the Division of Dockets Management (see ADDRESSES) in electronic or written form. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and on the Internet at <http://www.regulations.gov>.

#### V. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Fasano, A., and C. Catassi, "Current Approaches to Diagnosis and Treatment of Celiac Disease: An Evolving Spectrum," Gastroenterology, vol. 120, pp. 636-651, 2001.
2. National Institutes of Health (NIH), "NIH Consensus Development Conference Statement on Celiac Disease, June 28-30, 2004," Gastroenterology, vol. 128, pp. S1-S9, 2005.

3. Jabri, B., D.D. Kasarda, and P.H.R. Green, "Innate and Adaptive Immunity: The Yin and Yang of Celiac Disease," Immunological Reviews, vol. 206, pp. 219-231, 2005.
4. Molberg, O., N.S. Flaete, T. Jensen, et al., "Intestinal T-Cell Responses to High-Molecular-Weight Glutenins in Celiac Disease," Gastroenterology, vol. 125, pp. 337-344, 2003.
5. Farrell, R.J. and C.P. Kelly, "Celiac Sprue," The New England Journal of Medicine, vol. 346, pp. 180-188, 2002.
6. Fasano, A., I. Berti, T. Gerarduzzi, et al., "Prevalence of Celiac Disease in At-Risk and Not-At-Risk Groups in the United States: A Large Multicenter Study," Archives of Internal Medicine, vol. 163, pp. 286-292, 2003.
7. West, J., R.F.A. Logan, P.G. Hill, et al., "Seroprevalence, Correlates, and Characteristics of Undetected Coeliac Disease in England," Gut, vol. 52, pp. 960-965, 2003.
8. Green, P.H.R. and B. Jabri, "Coeliac Disease," Lancet, vol. 362, pp. 383-391, 2003.
9. Rubio-Tapia, A., R.A. Kyle, E.L. Kaplan, et al., "Increased Prevalence and Mortality in Undiagnosed Celiac Disease," Gastroenterology, vol. 137, pp. 88-93, 2009.
10. Catassi, C., I. Bearzo, and G.K.T. Holmes, "Association of Celiac Disease and Intestinal Lymphomas and Other Cancers," Gastroenterology, vol. 128, pp. S79-S86, 2005.
11. Corrao, G., G.R. Corazza, V. Bagnardi, et al., "Mortality in Patients With Coeliac Disease and Their Relatives: A Cohort Study," Lancet, vol. 358, pp. 356-361, 2001.
12. Waga, J., "Structure and Allergenicity of Wheat Gluten Proteins--A Review," Polish Journal of Food and Nutrition Sciences, vol. 13, pp. 327-338, 2004.
13. Vader, W., Y. Kooy, P. Van Veelen, et al., "The Gluten Response in Children With Celiac Disease Is Directed Toward Multiple Gliadin and Glutenin Peptides," Gastroenterology, vol. 122, pp. 1729-1737, 2002.

14. Kieffer, M., P.J. Frazier, N.W.R. Daniels, et al., "Wheat Gliadin Fractions and Other Cereal Antigens Reactive With Antibodies in the Sera of Coeliac Patients," Clinical and Experimental Immunology, vol. 50, pp. 651-660, 1982.

15. Sturgess, R.P., H.J. Ellis, and P.J. Ciclitira, "Cereal Chemistry, Molecular Biology, and Toxicity in Coeliac Disease," Gut, vol. 32, pp. 1055-1060, 1991.

16. Lundin, K.E.A., E.M. Nilsen, H.G. Scott, et al., "Oats Induced Villous Atrophy in Coeliac Disease," Gut, vol. 52, pp. 1649-1652, 2003.

17. Janatuinen, E.K., T.A. Kemppainen, R.J.K. Julkunen, et al., "No Harm From Five Year Ingestion of Oats in Coeliac Disease," Gut, vol. 50, pp. 332-335, 2002.

18. Haboubi, N.Y., S. Taylor, and S. Jones, "Coeliac Disease and Oats: A Systematic Review," Postgraduate Medicine Journal, vol. 82, pp. 672-678, 2006.

19. Office of Food Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration, "Health Hazard Assessment for Gluten Exposure in Individuals With Celiac Disease: Determination of Tolerable Daily Intake Levels and Levels of Concern for Gluten," May 2011.

20. Citizen Petition submitted by Michael Weber, June 2008, Docket No. FDA-2008-P-0333.

Dated: December 15, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.